

REMARKS

I. Statement of Substance of Interview

Applicants' representative, Michele Simkin, and Examiner Long discussed the number of claim groups as set forth in the restriction requirement dated September 23, 2010. Examiner Long confirmed that there were eight different groups of claims, and not six, and that the duplication of Roman numerals II and III in the Office Action was inadvertent.

II. Restriction Requirement

In the Office Action dated September 23, 2010 (and as clarified in the Summary of the Interview dated October 13, 2010), the Examiner restricted the claims into eight different groups as follows:

- Group I: claims 27-41, drawn to chimeric protein;
- Group II: claim 42, drawn to a nucleic acid molecule, perhaps comprising SEQ ID NOs: 1, 3, 33 or 40;
- Group III: claim 43, drawn to an expression vector;
- Group IV: claims 44-50, drawn to transgenic animal and its cells;
- Group V: claims 51-55, drawn to a method for detecting changes in calcium concentration;
- Group VI: claims 56-57 and 59, drawn to a method for detecting small chemical compound binding;
- Group VII: claim 58, drawn to a method of use; and
- Group VIII: claim 60, drawn to a diagnostic composition.

Applicants elect Group I, claims 27-41, drawn to chimeric protein, with traverse. Applicants traverse the restriction requirement on the grounds that the search and examination of the eight groups of claims is not unduly burdensome to the examiner.

In addition, Applicants traverse the restriction as set forth by the examiner and based on the teaching of EP 1238982 to Miyawaki et al. (Miyawaki). In the Office Action, the Examiner

asserts that “Miyawaki ... describes a modified calcium-binding polypeptide comprising: (a) a first chromophore, (b) troponin, and (c) a second chromophore, having a FRET donor/acceptor pair.” Office Action at page 4. Applicants respectfully disagree with the Examiner’s assessment of Miyawaki.

Miyawaki discloses a so-called “single fluorophore” calcium-indicator. The structure of these indicators differs from the FRET-based indicators disclosed in the present application in that the single fluorophore indicators use only a single chromophore (e.g. one fluorescent protein) instead of using two chromophores (e.g. two fluorescent proteins), namely a donor/acceptor pair suitable for FRET. One difference between these two types of indicators is that upon calcium binding to a “single fluorophore” indicator, the spectral properties of the single chromophore are altered (see Miyawaki at Figure 3). In contrast, with FRET-based indicators only the FRET-efficiency between a donor and an acceptor chromophore is changed – the spectral properties of the two individual chromophores remain unvaried. As a consequence, “single fluorophore” indicators change the emission intensity of one wavelength whereas FRET-based indicators change the emission intensity of two wavelengths.

Furthermore, the single chromophore used in the chimeric polypeptide as disclosed by Miyawaki is a so-called “circular permuted” variant, *i.e.* the N- and C-terminal parts of the wild type chromophore are interchanged at a defined position between amino acids 140 to 150 (Miyawaki at page 3, lines 35-38 (2) and 40-41 (4)). No such circular permuted variant is disclosed in the present application. Additionally the single fluorophore indicator described by Miyawaki makes use of a calcium-binding peptide (fused to the C-terminus of the circular permuted chromophore) and a target peptide of this calcium-binding peptide (fused to the N-terminus of the circular permuted chromophore). The FRET-based calcium indicator disclosed by the present application only makes use of a calcium-binding peptide that is fused between a donor/acceptor pair suitable for FRET.

Thus, contrary to the Examiner’s assertion, Miyawaki does not disclose troponin C/FRET chimeric polypeptides. Accordingly, Miyawaki does not teach the technical features of claim 27 as asserted by the Examiner. As such, the restriction is improper and should be withdrawn.

In the event that the restriction is maintained and deemed final, Applicants reserve the right to rejoin the non-elected method claims upon allowance of the composition claims.

III. Species Election Requirement

The Office Action also asserts that the “claims are directed to products and methods that require patentably distinct species of modified calcium-binding polypeptides,” and that applicants “must provide the required components of a particular modified calcium-binding polypeptide for examination.” Office Action at page 5. The Office Action continues, asserting that “[m]inimally, the applicant must specify: (a) a first chromophore type, (b) a troponin type, and (c) a second chromophore type.” *Id.* The Office Action also asserts that “[a]dditionally, if the elected species can also be described by a SEQ ID NO, the examiner requests designation of such identifier,” and that “[t]his is particularly relevant for claims 41 and 42.” Office Action at page 6.

For the species elections, Applicants elect (a) CFP as a first chromophore type; (b) human troponin C as a troponin type; and (c) YFP as a second chromophore type. Group I claims encompass the elected species. As claim 41 is within Group I, Applicants also elect SEQ ID NO: 2. With respect to claim 42 (which is in Group II), Applicants elect SEQ ID NO: 1 in the event the restriction requirement is withdrawn.

The species election is made with traverse on the grounds that the search and examination of the allegedly patentably distinct species is not unduly burdensome to the examiner. Applicants reserve the right to claim additional species which depend from or otherwise require all the limitations of an allowable generic claim.

IV. Conclusion

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of

papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

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